REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 22, 23, 30, 36, 37, 39 and 46 have been canceled without prejudice or disclaimer of the subject matter recited therein. Claims 8, 12, 14, 16, 19, 25, 28, 29, 31, 34, 35, 38, 40, 44, 45, 48 and 50 have been amended to further clarify Applicants' invention. Support for the amendments can be found throughout the specification. Specifically, support for claims 8, 25 and 31 can be found on page 6, lines 17-19, of the specification and support for claim 48 can be found in claim 12 and on page 11, lines 5-20, of the specification. Applicants reserve the right to pursue the deleted subject matter in subsequent continuation applications. Further, new claim 51 has been added. Support for new claim 51 can be found in claim 38. Accordingly, no new matter has been added.

I. Rejections under 35 U.S.C. § 112, first paragraph

Claims 22, 23 and 37 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, for the reasons of record. Specifically, the Examiner has stated that the specification does not enable for the intended use of the claimed pharmaceutical composition and method for preparing the same.

In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have canceled claims 22, 23 and 37 without prejudice or disclaimer of the subject matter recited therein.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 22, 23 and 37 under 35 U.S.C. § 112, first paragraph.

Claim 19 and new claims 40 and 41 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an isolated cell comprising the vector of claim 8 or a viral particle generated from said vector and an *in vitro* method of expressing one or more genes of interest into pluripotent cells comprising the step of transfecting or infecting said pluripotent cells with the vector of claim 8 or a viral particle generated from said vector or a pharmaceutical composition comprising the same, allegedly does not reasonably provide enablement for the same *in vivo* cell and the same method *in vivo*. Applicants respectfully traverse this rejection.

However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claims 19 and 40 to clarify that the cell of claim 19 is an isolated cell and the method of claim 40 is an *in vitro* method. Thus, as amended, the claims do not encompass both *in vitro* and *in vivo* methods for transfection or infection of pluripotent cells or *in vitro* and *in vivo* cells comprising a vector or a viral particle of the instant invention.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 19, 40 and 41 under 35 U.S.C. § 112, first paragraph.

Claim 39 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record.

In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have canceled claim 39 without prejudice or disclaimer of the subject matter recited therein.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 39 under 35 U.S.C. § 112, first paragraph.

Claims 14, 16, 28, 29, 34, 35, 44-45 and 50 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a vector or a retroviral vector for the expression of one or more genes of interest comprising a nucleotide sequence that is identical to SEQ ID NO:1 or SEQ ID NO:2 - (1) starting at nucleotide 1 and ending at nucleotide 578, (ii) starting at nucleotide 265 and ending at nucleotide 578 or (iii) starting at nucleotide 452 and ending at nucleotide 578- and methods of making the same, allegedly does not reasonably provide enablement for other embodiments of the claims. Applicants respectfully traverse this rejection.

However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claims 14, 16, 28, 29, 34, 35, 44-45 and 50 to no longer recite "substantially homologous."

Therefore, Applicants respectfully request withdrawal of the rejection of claims 14, 16, 28, 29, 34, 35, 44-45 and 50 under 35 U.S.C. § 112, first paragraph.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 8-19, 22-23, 25-39 and 42-50 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

Claims 8, 25, 31 and their dependent claims have been rejected for reciting the phrase "isolated from the 5' end of the genomic RNA of a type C retrovirus." The Examiner is not clear as to where the 3' end boundary of the nucleotide sequence is located. Further, the Examiner has stated that there is no clear and exact definition for the 5' end of the genomic RNA of a type C retrovirus in the specification. In addition, the Examiner has stated that the phrase "the DNA equivalent of said genomic RNA" is unclear.

In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claims 8, 25 and 31 to recite that the nucleotide sequence comprises all or part of the region which extends from the site of initiation of transcription up to the initiator codon of the gag gene of the virus.

The organization of type C retroviruses is described in basic books in the art. It is well known that the retroviral LTRs can be divided into three well characterized elements, U3, R and U5. As discussed on page 36 of Retroviruses (Coffin et al., Cold Spring Harbor Laboratory Press (1997)) enclosed herewith, U3 contains most of the transcriptional control elements (promoter, enhancer elements, etc.). R is derived from a sequence repeated at both ends of the RNA, and U5 is derived from the sequence unique to the 5' end of the RNA. From the definition of U3, R and U5, it follows that the site of transcription

initiation (position +1) is at the boundary between U3 and R. Therefore, at the filing date of the present application, the skilled person would have known that the site of initiation of transcription represents the first nucleotide which follows the U3 domain of the 5'LTR. Moreover, at the filing date of the present invention, the sequence of the vast majority of type C retroviruses was accessible to the skilled person from available literature or specialized data bank so that the skilled artisan could define the concerned region without undue experimentation. Concerning more specifically REV retrovirus, as discussed on page 22, lines 1-4, of the specification, the sequence extending from the transcription initiation site up to the initiator codon of the gag gene is disclosed in Darlix et al. (*J. Virol.*, 66:7245-52 (1992)) (enclosed herewith).

Furthermore, the Examiner has stated that the phrase "DNA equivalent of said genomic RNA" is unclear. Applicants submit that this phrase refers to the translation of an RNA sequence into a DNA sequence by replacing U nucleotides by T nucleotides in the sequence of the concerned genomic RNA. For example, if the sequence of the genomic RNA comprises AUCGUUA, the DNA equivalent will then comprise ATCGTTA.

Claim 12 has been rejected because the phrase "a third gene of interest" is unclear in the absence of any reference to a second gene of interest. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 12 to recite a first gene of interest in subpart c) and a second gene of interest (instead of third) in subpart (e).

Claim 48 has been rejected because the phrase "further comprises a first gene of interest" is unclear. In order to expedite prosecution in the subject application and not

acquiesce to the Examiner's rejection, Applicants have amended claim 48 to specifying all of the structural elements present in the claimed retroviral vector. Support for the proposed amendment can be found in originally filed claim 12 and page 11, lines 5-20 of the specification.

Claims 14, 16, 28, 29, 34, 35, 44 and 45 have been rejected because the phrase "substantially homologous" allegedly is not defined by the claim or the specification. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claims 14, 16, 28, 29, 34, 35, 44-45 and 50 to no longer recite "substantially homologous."

Claim 38 has been rejected because the Examiner is not clear as to what is encompassed by the phrase "by the recombination route." In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 38 to no longer recite "by the recombinant routes" but instead recite "by recombinant techniques" which is equivalent in the art.

Claim 39 has been rejected for allegedly not reciting all essential steps required for the production of a transgenic animal. This portion of the rejection is rendered moot in light of the cancellation of claim 39.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 8-19, 22-23, 25-39 and 42-50 under 35 U.S.C. § 112, second paragraph.

III. Rejections under 35 U.S.C. § 102

Claims 8-10, 12, 18, 19, 22, 25 and 31 have been rejected under 35 U.S.C.

§ 102(b) as allegedly being anticipated by Berlioz et al. (*J. Virol.* 69:6400-7, 1995) for the reasons of record. Applicants respectfully traverse this rejection.

It is well settled law that to anticipate a claim, a single reference must teach each and every element of the claim, and the single reference must be enabling. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); *Atlas Powder Co. v. E.I du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

Berlioz et al. relates to murine sarcoma viruses (MSV), and more particularly to Harvey murine sarcoma virus (HaMSV). Berlioz et al. identified an IRES site contained in the 5' end of the HaMSV genomic RNA, between positions 205 to 794. Transfection studies demonstrated that this HaMSV sequence (designated VL30), when located between two cistrons in a retroviral vector, can promote both internal initiation of translation of the second cistron and packaging of genomic RNA into retroviral particles. Berlioz et al. fails to teach the presence of an IRES sequence in the 5'end of a REV genomic RNA as recited in amended claim 8, 25 and 31.

Claims 8, 25 and 31 have been amended to be drawn to a vector using a nucleotide sequence isolated from the 5' end of the genomic RNA of a reticuloendotheliosis virus (REV) or from the DNA equivalent thereof. This amendment finds support at least page 7, lines 6-9 of the specification.

Therefore, because Berlioz et al. does not teach each and every element of the claimed invention, Berlioz et al. does not anticipate the claimed invention.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 8-10, 12, 18, 19, 22, 25 and 31 under 35 U.S.C. § 102(b).

IV. Rejections under 35 U.S.C. § 103

Claims 8, 10, 11, 12, 17, 22, 23, 38, 40-41, 47 and 48 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Berlioz et al. (U.S. Patent No. 5,925,565) in view of Berlioz et al. (*J. Virol.* 69: 6400-7 (1995)) for the reasons of record. Applicants respectfully traverse this rejection.

Berlioz et al. (US patent 5, 925,565) teaches a new IRES site present in the murine (rat or mouse) VL30 retrotransposon. This sequence permits translation initiation in a cap independent manner of the second cistron in the context of polycistronic vectors. Moreover, in the context of a retroviral vector, it also discharges the function of dimerization and encapsulation, independently of its position in the vector.

The Examiner points out that the rat VL30 region was isolated from the 5' end of the HaMSV genomic RNA, as mentioned in Berlioz et al. (1995, J. Virol. 69, 6400-6407).

Amendments introduced in claim 8 in response to novelty rejections should overcome obviousness rejections since the cited reference fails to teach the use of a sequence isolated from the 5' end of REV genomic RNA as IRES to initiate translation initiation from a downstream gene sequence. Indeed, Berlioz et al. references (1995, J. Virol. 69, 6400-6407 and US patent 5, 925,565) relate to a murine sarcoma virus which is quite distinct from an REV virus (absence of any significant sequence homology between the VL30 IRES disclosed in Berlioz et al. and the sequence of the present invention).

Thus, a person skilled in the art would not be motivated to use REV-isolated sequences for efficient translation of a cistron positioned downstream of said REV sequence.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 8, 10, 11, 12, 17, 22, 23, 38, 40-41, 47 and 48 under 35 U.S.C. § 103.

Claim 17 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Berlioz et al. (*J. Virol.* 69: 6400-7 (1995) in view of Dirks et al. (U.S. Patent No. 6,060,273) for the reasons of record.

As discussed above, Berlioz et al. (1995) relates to the identification of an IRES site in the 5' end of HaMSV genomic RNA. Dirks et al. discloses recombinant plasmid and viral dicistronic vectors in which internal translation initiation of the second cistron is controlled by an IRES. Suitable IRES sites include those of encephalomyocarditis virus (EMCV), Theiler's murine encephalomyelitis virus (TMEV), foot and mouth disease virus (FMDV), bovine enterovirus (BEV), Coxsackie B virus (CBV), and human rhinovirus (HRV), the human immunoglobulin heavy chain binding protein (BIP), the Drosophila ultra-bithorax and, as absolute preference, the poliovirus type 1 (see column 6 lines 17-32). Dirks et al. fails to teach or mention the presence of an IRES site within the 5'end of an REV genomic RNA.

Accordingly, there is no element of the presently claimed invention which is suggested or specifically disclosed in the cited prior art documents taken either individually or in combination.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 17 under 35 U.S.C. § 103.

Claims 8, 10, 12, 13 and 48 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Berlioz et al. (U.S. Patent No. 5,925,565) in view of Berlioz et al. (*J. Virol.* 69: 6400-7 (1995) as applied to claims 8, 10, 11, 12, 17, 22, 23, 38, 47 and 48 above, and further in view of Sands et al. (U.S. Patent No. 6,136,566).

Claim 13 is drawn to a retroviral vector comprising two expression cassettes, the first one containing a gene of interest placed under the control of the retroviral 5' LTR and the second one driven by an internal promoter being bicistronic with translation reinitiation mediated by an REV-isolated sequence and being in opposite orientation relative to the transcription direction exhibited by the retroviral LTR.

The discussion above regarding Berlioz et al. is incorporated herein by reference.

Sands et al. relates to the construction of libraries of genetically altered cells and vectors that may be used to generate such libraries. One vector contemplated is a retroviral vector for inserting a selectable marker into cell transcripts that comprise a promoter element, the selectable marker sequence and a splice donor. The direction of the transcription of the selectable marker is opposite to that of the direction of the normal retrovirus transcription to avoid interference with transcription of the retroviral genome in the packaging cell lines (which reduces retroviral titers). Sands et al. fails to teach or suggest bicistronic retroviral vectors using an REV-isolated sequence to promote efficient translation of the second cistron.

Applicants submit that none of the cited references, alone or in combination, teach or suggest the claimed invention.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 8, 10, 12, 13 and 48 under 35 U.S.C. § 103.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned agent concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Teresa Stanek Rea
Registration No. 30,427

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: November 15, 2001

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Attachment to Amendment dated November 15, 2001
Marked-up Claims 8, 12, 14, 16, 19, 25, 28, 29, 31, 34, 35, 38, 40, 44, 45, 48 and 50

8. (Three Times Amended) A vector for the expression of one or more genes of interest comprising a nucleotide sequence isolated from the 5' end of the genomic RNA of a [type C retrovirus selected from the group consisting of REV and MSV] reticuloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA, wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation codon of the gag gene.

12. (Three Times Amended) The retroviral vector according to claim 10, comprising at least:

(a) a retroviral 5' LTR,

(b) an encapsidation region,

(c) a first gene of interest,

(d) an IRES site,

(e) a [third] second gene of interest, and

(f) a retroviral 3' LTR,

at least one of the encapsidation region and the IRES site consisting of said nucleotide sequence.

14. (Twice Amended) The retroviral vector according to claim 12, in which the encapsidation region is derived from a murine retrovirus, or from a VL30-type

retrotransposon and the IRES site comprises a nucleotide sequence which is [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO: 2 or to the DNA equivalent of said sequence:

(i) starting at nucleotide 1 and ending at nucleotide 578,

(ii) starting at nucleotide 265 and ending at nucleotide 578, or

(iii) starting at nucleotide 452 and ending at nucleotide 578.

16. (Twice Amended) The retroviral vector according to claim 10, comprising a retroviral 5' LTR derived from an REV virus, a retroviral 3' LTR of any origin, one or more genes of interest, and a nucleotide sequence which is [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO: 2 or to the DNA equivalent of said sequence starting at nucleotide 1 and ending at nucleotide 578.

19. (Three Times Amended) [A] An isolated cell comprising a vector or infected with a viral particle generated from a viral vector according to claim 8.

25. (Amended) A method for providing an internal ribosome entry site (IRES) to a vector for the transfer and expression of one or more genes of interest, comprising the step of introducing into said vector a nucleotide sequence isolated from the 5' end of the genomic RNA of a [type C retrovirus selected from the group consisting of REV and MSV] reticuloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA.

wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation codon of the gag gene.

28. (Amended) The method of claim 27, wherein said nucleotide sequence comprises at least 100 nucleotides and at most 800 nucleotides [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO:1 or to the DNA equivalent of said sequence.

29. (Amended) The method of claim 28, wherein said nucleotide sequence is [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO:2 or to the DNA equivalent of said sequence:

(i) starting at nucleotide 1 and ending at nucleotide 578,

(ii) starting at nucleotide 265 and ending at nucleotide 578, or

(iii) starting at nucleotide 452 and ending at nucleotide 578.

31. (Amended) A method of allowing or activating the encapsidation of a retrovirus or of a retroviral vector, comprising the step of introducing into said retrovirus or retroviral vector, a nucleotide sequence isolated from the 5' end of the genomic RNA of a [type C retrovirus selected from the croup consisting of REV and MSV] reticuloendotheliosis virus (REV) or from the DNA equivalent of said genomic RNA, wherein said nucleotide sequence comprises all or part of the region of said 5' end which extends from the site of initiation of transcription up to the initiation codon of the gag gene.

34. (Amended) The method of claim 33, wherein said nucleotide sequence comprises at least 100 nucleotides and at most 800 nucleotides [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO:1 or to the DNA equivalent of said sequence.

35. (Amended) The method of claim 34, wherein said nucleotide sequence is [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO:2 or to the DNA equivalent of said sequence:

(i) starting at nucleotide 1 and ending at nucleotide 578,

(ii) starting at nucleotide 265 and ending at nucleotide 578, or

(iii) starting at nucleotide 452 and ending at nucleotide 578.

38. (Amended) A method for the preparation of one or more polypeptides of interest by [the] recombination [route] techniques, comprising the step of culturing in vitro a cell comprising a vector according to claim 8 [or infected with a viral particle according to claim 18] and harvesting said polypeptide(s) from the supernatant or from the cell culture.

40. (Amended) [A] An in vitro method for expressing one or more genes of interest into pluripotent cells, comprising the step of transfecting or infecting said pluripotent cells with a vector or a viral particle generated from a viral vector according to claim 8 or a pharmaceutical composition prepared from said vector or viral particle.

44. (Amended) The vector of claim 43, wherein said nucleotide sequence comprises at least 100 nucleotides and at most 800 nucleotides [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO:1 or to the DNA equivalent of said sequence.

45. (Amended) The vector of claim 44, wherein said nucleotide sequence is [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO:2 or to the DNA equivalent of said sequence:

(i) starting at nucleotide 1 and ending at nucleotide 578,

(ii) starting at nucleotide 265 and ending at nucleotide 578, or

(iii) starting at nucleotide 452 and ending at nucleotide 578.

48. (Amended) The retroviral vector according to claim [12] 10, wherein said vector [further] comprises [a first gene of interest followed by an internal promoter region with a different origin from that of said retroviral 5' LTR] :

a) a retroviral 5' LTR,

b) an encapsidation region,

c) a first gene of interest,

d) an internal promoter region of a different origin from that of said retroviral 5' LTR,

e) a second gene of interest,

f) an IRES site,

g) a third gene of interest, and

h) a retroviral 3' LTR,

at least one of the encapsidation region and the IRES site consists of said nucleotide sequence.

50. (Amended) The retroviral vector according to claim 16, comprising a retroviral 5' LTR derived from a REV virus, a retroviral 3' LTR of any origin, one or more genes of interest, and a nucleotide sequence which is [substantially homologous or] identical to the sequence presented in the sequence identifier SEQ ID NO:2 or to the DNA equivalent of said sequence, starting at nucleotide 265 and ending at nucleotide 578 as encapsidation region.